REMARKS

Statement Of The Substance Of The Interview

Applicants thank Examiner Steele for the helpful telephonic interview on October 19, 2009 with Applicants' representatives, Laura A. Coruzzi and Jacqueline Benn, during which the pending rejections under 35 U.S.C. § 112, second paragraph and for obviousness-type double patenting were discussed.

During the interview, Examiner Steele indicated that the claim amendments discussed would overcome the indefiniteness rejection under 35 U.S.C. § 112, second paragraph. Moreover, Examiner Steele agreed to consider further amendments to address the rejection for obviousness-type double patenting.

Entry of this Statement Of The Substance Of The Interview into the file of this application is respectfully requested.

Claims

Claims 125, 126, 128, 131-138, and 142-160 are currently pending and under consideration. Claims 145-160 have been canceled. Applicants have amended claims 125 and 126 and have added new claims 161-168 to clarify the presently claimed invention and expedite allowance of the claims. No new matter has been added by these amendments. Upon entry of the present amendments, claims 125, 126, 128, 131-138, 142-144, and 161-168 will be pending in the present application.

Objection

The Examiner has objected to claim 132 because the status identifier of "Presently Amended" should be "Previously Presented." The status identifier of claim 132 has been amended to recite "Previously Presented." Accordingly, the objection to claim 132 should be withdrawn.

Rejections

I. The Indefiniteness Rejections Under 35 U.S.C. § 112, Second Paragraph Is Obviated and Should Be Withdrawn

Claims 126, 148, 152, 156 and 160 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite, with respect to the phrase "n is an integer preferably selected from about 3 to about 20". Claims 145, 149, 153, and 157 are also rejected under 35 U.S.C. § 112, second paragraph, as indefinite, with respect to the phrase "such as".

Claims 145-160 have been cancelled, without prejudice to the applicant's right to pursue the subject matter in other applications. Therefore, the rejection of claims 145, 148, 149, 152, 153, 156, and 157 is rendered moot.

Without admitting to the propriety of the rejection, claim 125 has been amended to delete the phrase "such as" and to insert the phrase "including". Without admitting to the propriety of the rejection, claim 126 has been amended to recite "n is an integer from about 3 to about 20," as suggested by the Examiner. Applicants submit that the indefiniteness rejection is obviated in view of the claim amendments.

For the foregoing reasons, Applicants respectfully request withdrawal of the indefiniteness rejection of the claims under 35 U.S.C. § 112, second paragraph.

II. Double Patenting

The Double Patenting Rejection Of Claims 125, 126, 128, 131-138, and 142-160 Over Claims 1-18 of U.S. Patent No. 5,876,727, alone or in combination with U.S. Patent No. 5,601,831 Should Be Withdrawn

Claims 125, 126, 128, 131-138, and 142-160 are rejected on the ground of nonstatutory obviousness-type double patenting as being obvious over claims 1-18 of U.S. Patent No. 5,876,727 (the "'727 patent"), alone or in combination, with U.S. Patent No. 5,601,831 to Green ("Green"). For the following reasons, Applicants submit that the obviousness-type double patenting rejection should be withdrawn.

In rejecting the claims of the present invention, the Examiner cites to Figures 17b and 18, and column 13, lines 45-49 of the '727 patent. An obviousness-type double patenting rejection must be based on a comparison of the claims of an application against the claims of another patent or application (*see* M.P.E.P. § ("[a] nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is either anticipated by, or would have been obvious over the reference claim(s)") (M.P.E.P. § 804, 8th Ed., Revision 7, July 2008; emphasis added). Thus, the Examiner improperly relies on the specification, *i.e.*, not the claims, of an application in rejecting the claims based on obviousness-type double patenting.

Moreover, in contrast to the presently claimed invention, the '727 patent does not claim the use of a pseudomonas exotoxin as a carrier. The Examiner attempts to overcome this omission by citing Green. Green teaches the use of protein "e" and peptides having protein "e" epitopes for vaccination against nontypable and typable *H. Influenzae* (*see* Green, col. 1, lines 62-64). While Green describes that when a haptenic peptide of protein "e" is

used, it can be conjugated to an immunogenic carrier molecule (*see* Green, col. 11, lines 16-25); the conjugates of Green are distinct from the hapten-carrier conjugates of the instant invention. Protein "e" is a highly conserved and immunogenic lipoprotein of the bacteria *H. Influenzae*, having a molecular weight of about 28 kDa (*see* Green, col. 1, lines 57-62; col. 3, lines 9-15 and lines 18-33; and Figures 7A-7B). As described previously, nicotine is a small molecule hapten that has been shown to suppress the immune response. Thus, in contrast to protein "e," nicotine is not a peptide or protein and is not immunogenic. Additionally, Green describes the use of carriers such as pseudomonas exotoxin only in the context where protein "e" or peptides having protein "e" epitopes are administered as multivalent subunit vaccines in combination with *other* antigens of *H. Influenzae* (*see* Green, col. 11, lines 34-39). That is, Green describes the use of a carrier protein, such as pseudomonas exotoxin, in a multivalent subunit vaccine where an immune response is induced against a plurality of different antigens of *H. Influenzae*. By contrast, the hapten-carrier conjugates of the instant invention elicit an immune response to a single antigen, *i.e.*, nicotine. Therefore, the conjugates of Green are distinct from the hapten-carrier conjugates of the instant invention. Based on Green, one of skill in the art would not know to conjugate pseudomonas exotoxin with nicotine.

The claimed invention is not rendered obvious by the cited art, in part, because the cited art, taken alone or in combination, fails to describe or suggest all of the claim limitations. *Graham*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Thus, the Examiner has failed to establish a case of *prima facie* obviousness. However, assuming *arguendo*, that a *prima facie* case of obviousness has been made, the Applicants invite the Examiner's attention to the unexpected advantageous and/or superior properties associated with the claimed conjugates. (A *prima facie* case of obviousness is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. *In re Chupp*, 816 F.2d 643, 646; 2 U.S.P.Q.2d 1437, 1439 (Fed Cir 1987)). In particular, Applicants direct the Examiner's attention to Hatsukami *et al.*, "Safety and Immunogenicity of a Nicotine Conjugate Vaccine in Current Smokers" Clin. Pharmacol. Ther. 76: 456-67 (2005) (reference C82 of the Supplemental IDS filed June 12, 2008). Hatsukami describes the surprising properties of an aminomethylnicotine conjugated to psuedomonas exotoxin (NicVAX). NIC-VAX is an example of a nicotine derivative-pseudomonas exotoxin conjugate formulated as an anti-nicotine vaccine that is currently in clinical trials for smoking cessation in humans.

The Phase II clinical trial results for NicVAX demonstrate that nicotine-pseudomonas exotoxin conjugate induces a nicotine-specific antibody response (*see* Hatsukami *et al.*, "Safety and Immunogenicity of a Nicotine Conjugate Vaccine in Current Smokers" Clin. Pharmacol. Ther. 76: 456-67 (2005) (reference C82 of the Supplemental IDS filed June 12, 2008)). The trials show a clear dose response relationship between dose of nicotine conjugate and mean concentration of nicotine-specific antibodies in serum (*see*, Hatsukami *et al.*, at page 464, right col., first full paragraph, and Figures 1 and 3). This study demonstrated that 6 out of 16 patients who received the vaccine at a dose of 200 μg were able to abstain from smoking cigarettes for at least 30 days during the study, as compared to 2 out of 23 patients that received placebo. These clinical trial results indicate that nicotine conjugated to a pseudomonas exotoxin carrier can be used efficaciously as a vaccine to elicit an antibody response to nicotine to treat nicotine addiction. Thus, these clinical trial results support the unexpected advantageous properties associated with the claimed conjugates.

For the foregoing reasons, one of skill in the art, armed with the '727 patent, with or without Green, would not arrived at the claimed invention. Accordingly, Applicants respectfully request withdrawal of the obviousness-type double patenting rejection of claims 125, 126, 128, 131-138, and 142 over claims 1-18 of the '727 patent, alone or in combination, with Green.

New Claims 161-168 are Patentable Over Claims of the '727 Patent Alone, or in Combination With Green

New claims 161-168 are directed to nicotine conjugated to pseudomonas exotoxin – in particular nicotine modified to contain the CJ 11.1 branch.

Neither the pseudomonas exotoxin carrier nor the CJ 11.1 linker are specified in the claims of the '727 patent. This defect is not by cured by the disclosure of the '727 patent or the secondary reference, Green. Therefore, Applicants respectfully submit that *prima facie* obviousness as to the claims, as amended, should not be found.

However, assuming *arguendo*, that a *prima facie* case of obviousness is found, the Applicants invite the Examiner's attention to the evidence of record showing unexpected advantageous and/or superior properties associated with the claimed conjugates. (A *prima facie* case of obviousness is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. *In re Chupp*, 816 F.2d 643, 646; 2 U.S.P.Q.2d 1437, 1439 (Fed Cir 1987)).

As previously indicated in this record, nicotine is a small non-immunogenic hapten that actually *suppresses* the immune response. Thus, one of skill in the art would not have expected nicotine-carrier conjugates to induce a nicotine-specific immune response (*see* specification, page 19, lines 13-19; page 57, lines 31-35; and page 103, lines 32-34; *see also* Geng *et al.*, "Effects of Nicotine on the Immune Response I: Chronic Exposure to Nicotine Impairs Antigen Receptor-Mediated Signal Transduction in Lymphocytes," Toxicol. Appl. Pharmacol. 135:268-278 (1995) (reference C93 of the Supplemental IDS filed January 26, 2009), Abstract and Discussion section at page 75, 3rd paragraph)).

The evidence in this record shows that the claimed compositions unexpectedly induce a nicotine-specific immune response in human subjects. As discussed above, Hatsukami describes the surprising properties of an aminomethylnicotine conjugated to pseudomonas exotoxin (NicVAX), *i.e.*, nicotine conjugated to CJ 11.1 as currently claimed. As discussed above, the Phase II clinical trials for NicVAX show that the aminomethylnicotine-pseudomonas exotoxin conjugate vaccine induces a nicotine-specific antibody response in human subjects (*see* Hatsukami) and that there is a clear dose response relationship between dose of conjugate vaccine and mean concentration of nicotine-specific antibodies in serum (*see*, Hatsukami *et al.*, at page 464, right col., first full paragraph, and Figures 1 and 3). This study demonstrated that 6 out of 16 patients who received the vaccine were able to abstain from smoking cigarettes for at least 30 days during the study, as compared to 2 out of 23 patients that received placebo. This clinical trial demonstrates the surprising result that aminomethylnicotine conjugated to a pseudomonas exotoxin can be used efficaciously as a vaccine to elicit an antibody response to nicotine to treat nicotine addiction. Thus, these clinical trial results support the unexpected advantageous properties associated with the claimed conjugates.

For the foregoing reasons, Applicants respectfully assert that claims 161-168 are patentable over claims 1-18 of the '727 patent, alone or in combination, with Green.

The Provisional Double Patenting Rejection Of Claims 125, 126, 128, 131-138, and 142-160 Over Claims 88, 90, 103, 106, 108, 109, and 128-135 Of Copending U.S. Patent Application No. 11/472,215 Should Be Withdrawn

Claims 125, 126, 128, 131-138, and 142-160 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 88, 90, 103, 106, 108, 109, and 128-135 of copending U.S. Patent Application No. 11/472,215. During our April 30, 2009 telephonic interview, the Examiner indicated that since Application No. 11/472,215 is still pending, upon a finding of allowable subject matter, this application will be allowed to issue.

The Provisional Double Patenting Rejection Of Claims 125, 126, 128, 131-138, and 142-160 Over Claims 119-135 Of Copending U.S. Patent Application No. 11/472,220 Should Be Withdrawn

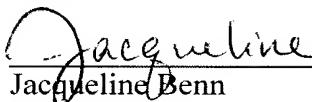
Claims 125, 126, 128, 131-138, and 142-160 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 119-135 of copending U.S. Patent Application No. 11/472,220. During our April 30, 2009 telephonic interview, the Examiner indicated that since Application No. 11/472,220 is still pending, upon a finding of allowable subject matter, this application will be allowed to issue.

CONCLUSION

Applicants respectfully request that the Examiner consider the amendments and the remarks made herein, and that the Examiner enter them into the record for the present application. Withdrawal of all rejections and an allowance is earnestly sought. The Examiner is invited to contact the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

Date: November 4, 2009



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